JACC: CARDIOVASCULAR INTERVENTIONS VOL. 2, NO. 11, 2009

ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2009.08.016

Enoxaparin Versus Unfractionated Heparin in Elective Percutaneous Coronary Intervention

1-Year Results From the STEEPLE (SafeTy and Efficacy of Enoxaparin in Percutaneous coronary intervention patients, an internationaL randomized Evaluation) Trial

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Objectives Our purpose was to evaluate long-term mortality and identify factors associated with 1-year mortality in patients who underwent elective percutaneous coronary intervention (PCI).

Background While long-term outcomes in PCI patients have been reported previously, limited data are currently available regarding the comparative long-term outcomes in PCI patients who receive enoxaparin versus intravenous unfractionated heparin (UFH).

Methods We conducted a follow-up analysis of clinical outcomes at 1 year in patients enrolled in the STEEPLE (SafeTy and Efficacy of Enoxaparin in Percutaneous coronary intervention patients, an internationaL randomized Evaluation) trial of 3,528 patients undergoing elective PCI. Patients were randomized to receive either intravenous 0.50-mg/kg or 0.75-mg/kg enoxaparin or intravenous UFH during elective PCI procedures. All-cause mortality at 1 year after index PCI was the main outcome measure.

Results Mortality rates were 1.4%, 2.0%, and 1.5% from 1 month to 1 year, and 2.3%, 2.2%, and 1.9% from randomization to 1 year, after index PCI in patients receiving 0.50 mg/kg enoxaparin, 0.75 mg/kg enoxaparin, and UFH, respectively. Multivariate analysis identified nonfatal myocardial infarction and/or urgent target vessel revascularization up to 30 days after index PCI (hazard ratio: 3.5, 95% confidence interval: 1.7 to 7.3; $p < 0.001$), and major bleeding within 48 h (hazard ratio: 3.0, 95% confidence interval: 1.1 to 8.5; $p = 0.04$) as the strongest independent risk factors for 1-year mortality.

Conclusions The 1-year mortality rates were low and comparable between patients receiving enoxaparin and UFH during elective PCI. Periprocedural ischemic or bleeding events were the strongest independent predictors of 1-year mortality. (The STEEPLE Trial; NCT00077844) (J Am Coll Cardiol Intv 2009;2:1083–91) © 2009 by the American College of Cardiology Foundation

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Manuscript received April 7, 2009; revised manuscript received August 7, 2009, accepted August 10, 2009.

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NOVEMBER 2009:1083–91

The safety and efficacy of intravenous low-molecular-weight heparin (LMWH) anticoagulation in patients undergoing either emergent or elective percutaneous coronary intervention (PCI) has previously been demonstrated in a number of trials (1–8). The largest of these trials in elective PCI was the STEEPLE (SafeTy and Efficacy of Enoxaparin in PCI patients, an internationaL randomized Evaluation) trial, which was a prospective, open-label, parallel-group study

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evaluating intravenous enoxaparin (0.50 mg/kg or 0.75 mg/kg) and unfractionated heparin (UFH) in patients with stable coronary artery disease (7). The study found that enoxaparin was associated with reduced bleeding rates, compared with UFH. Notably, the beneficial effect of enoxaparin was primarily driven by a significant 57% reduction in noncoronary artery bypass graft-related major bleeding in the first 48 h compared with UFH (7). Although the STEEPLE study was not powered to make definitive conclusions regarding efficacy, a subsequent meta-analysis of 13 randomized studies, which was sufficiently powered, reported similar efficacy between UFH and LMWH (6).

However, none of 13 published randomized studies has examined the long-term outcomes of PCI in patients receiving intravenous LMWH or UFH. In this study, we present data from a 1-year follow-up of the STEEPLE trial, during which we evaluated patient outcomes and identified factors associated with long-term mortality.

Abbreviations and Acronyms

ACS = acute coronary syndromes
ACT = activated clotting time
CI = confidence interval
CK = creatine kinase
CK-MB = creatine kinase-myocardial/brain mass
HR = hazard ratio
LMWH = low-molecular-weight heparin
MI = myocardial infarction
PCI = percutaneous coronary intervention
UFH = unfractionated heparin
ULNR = upper limit of the normal range
UTVR = urgent target vessel revascularization

Methods

Between January 2004 and December 2004, a total of 3,528 patients were enrolled into the STEEPLE trial. Briefly, 1,070 were randomly assigned to receive enoxaparin 0.50 mg/kg intravenously, 1,228 to enoxaparin 0.75 mg/kg intravenously, and 1,230 to activated clotting time (ACT)-adjusted UFH (7). Randomization was stratified according to the medical center and planned use of glycoprotein IIb/IIIa inhibitors. Regardless of weight or renal function, patients were eligible for the study if they were age ≥17 years, were scheduled to undergo elective PCI with a femoral approach, did not meet any of the exclusion criteria, and gave informed consent. The exclusion criteria included recent thrombolysis, a planned staged procedure, an increased risk of bleeding, treatment with a parenteral antithrombotic agent before PCI, or a known hypersensitivity to the drugs used in the study. The study complied with the Declaration of Helsinki, and locally appointed ethics committees approved the research protocol.

A follow-up analysis of clinical outcomes in patients enrolled in the STEEPLE trial, which was not part of the original study protocol, was initiated in December 2005—1 year after the closure of the primary study. From the original 124 centers, 25 did not participate in this analysis and 892 patients were lost to follow-up beyond day 30. Reasons for the loss of follow-up data were: no internal review board approval (n = 154); contractual issues (n = 435); lengthy administrative procedures (n = 115); unwillingness to participate (n = 113); other reasons (n = 75).

Treatment protocol. Patients were treated with aspirin (75 to 500 mg/day) and thienopyridines according to local practice. Before PCI, 46% of patients had received long-term treatment with thienopyridine. On the day of PCI, approximately 40% of patients in each treatment arm had received a glycoprotein IIb/IIIa inhibitor and 94% a thienopyridine. Patients in the control arm, who were not receiving concurrent glycoprotein IIb/IIIa inhibitors, were given an initial intravenous bolus of 70 to 100 IU/kg UFH to achieve a target ACT of 300 to 350 s. Patients who received concurrent glycoprotein IIb/IIIa inhibitors were given an initial bolus of 50 to 70 IU/kg of UFH to achieve a target ACT of 200 to 300 s. Additional boluses of UFH (before the start of PCI and during the procedure) were given to 16.5% of patients when ACT measurements dropped below the recommended range. Patients receiving enoxaparin were not routinely monitored for anticoagulation levels, and neither dose regimen was adjusted according to the concomitant use of glycoprotein IIb/IIIa inhibitors.

In the original study, a nonsignificant increase in mortality up to 30 days after index PCI was observed in patients receiving 0.50 mg/kg enoxaparin, compared with UFH, which resulted in early closure of the low-dose enoxaparin arm (7).

End points at 1 year. The primary end point for this analysis was all-cause mortality at 1 year. Data on all-cause mortality at 1 year were gathered by telephone or by visiting participating sites; no information on cause of mortality or other adverse events was collected.

Statistical analyses. All-cause mortality at 1 year was analyzed using a Cox proportional hazard model. All patients enrolled in the initial STEEPLE trial, whatever the duration of follow-up, were included in this model. Each enoxaparin dose was compared with UFH separately. The Simes adjustment for multiplicity was applied to ensure a global type 1 error rate of 0.05: if both p values were 0.05 or